REMARKS:

Upon entry of the Amendment above, claims 1-4, 8-10, 15, 18-42, 54-67, 130-168 and 170-199 will be pending in this application. By this Amendment, claims 1, 54, 198 and 199 are amended, and claims 17 and 169 are cancelled. No new matter has been added by this amendment.

Rejection under 35 U.S.C. §102

Claims 1-5, 8-10, 15, 17, 54-65 and 139-199 have been rejected under 35 U.S.C §102(b) as allegedly being anticipated by Rezai (US 2002/0116030), or in the alternative, under 35 U.S.C §103(a) as allegedly being obvious over Rezai. Applicant traverses the rejection to the extent it is maintained.

The Office Action appears to state that Rezai inherently discloses inhibition of a release of a proinflammatory mediator in a subject suffering from, or at risk of, a disease or disorder mediated by a proinflammatory mediator because Rezai teaches stimulating a sympathetic neuron which would inherently result in inhibiting release of such a mediator. The Office Action further states that Rezai discloses treatment of a patient at risk of or suffering from burns or spinal cord injury (citing paragraphs 50-51) and states that it is inherent that such diseases or disorders are mediated by an inflammatory cytokine cascade.

However, it appears that the Office Action is misinterpreting the teachings of Rezai. At paragraphs 50-51, Rezai discusses complex regional pain syndrome (CRPS), also known as reflex sympathetic dystrophy syndrome, and symptoms and precipitating factors of CRPS. While Rezai does state at paragraph 50 that pain associated with CRPS has been described as "burning", Rezai fails to teach or suggest treating a burn patient. Further, at paragraph 51, Rezai states that spinal cord lesions may be a precipitating factor of CRPS. However, Rezai does not teach or suggest treating a patient suffering from a spinal cord injury. Rather, Rezai teaches treating a patient suffering from CRPS. Contrary to the assertion set forth in the Office Action, Rezai does not appear to teach or suggest treating a patient suffering from or at risk of a disorder mediated by the immune response.

In the present application, the inventor has recognized for the first time that stimulation of a sympathetic neuron, particularly the splenic nerve, can attenuate an immune response. Rezai is devoid of any teaching that stimulation of a sympathetic neuron can result in attenuation of an

immune response, inhibition of release of a pro-inflammatory mediator, or the like. The Office Action appears to recognize fact at lines 4-6 of page 3, stating that the method of Rezai is not explicitly disclosed to inhibit the release of a proinflammatory mediator.

As there is no teaching or suggestion in Rezai that stimulation of a sympathetic neuron can result in attenuating an immune response, inhibiting release of a proinflammatory mediator, or the like, and as Rezai fails to expressly disclose or suggest that the methods of Rezai could be applied to subjects at risk of, or suffering from, diseases or disorders mediated by an immune response, a proinflammatory mediator, or the like, one would not apply the teachings of Rezai to a subject suffering from or at risk of a disease mediated by an immune response.

Accordingly, Rezai does not anticipate or render obvious claims 1-5, 8-10, 15, 17, 54-65 and 139-199. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103

1. Rezai

Claims 63-67 have been rejected under 35 U.S.C §103(a) as allegedly being obvious over Rezai. Applicant traverses the rejection to the extent it is maintained.

Claims 63-67 depend from independent claim 54, which as discussed above is not obvious in light of Rezai. Thus, for at least the reasons stated above, claims 63-67 are also not obvious in light of Rezai.

Further, the Office Action states that while Rezai does not disclose stimulation of an end organ, it would have been obvious to do so. The Office Action further states that Applicant has not disclosed that such end organ stimulation provides an advantage, is used for a particular purpose, or solves a stated problem. In addition, the Office Action states that one would have expected end organ stimulation to be as effective as sympathetic nerve stimulation because end organ stimulation is an obvious design choice. On all accounts (other than the fact that Rezai does not teach end organ stimulation), Applicants assert that the Office Action is either incorrect or inaccurate.

Rezai discloses advantages of stimulation of sympathetic ganglia to achieve "wide and far reaching effects" (see last sentence of paragraph 26). Thus, one would not be drawn to stimulation of an end organ based on the teachings Rezai, as one would expect a much more narrow and short

reaching effects. Further, the present application states that it may be desirable to reduce non-specific or undesired effects by stimulating downstream of a ganglia (see paragraph 59 of the published application) and further states that end organ stimulation may be effective when immediate attenuation of an immune response is desired (see paragraph 60 of the published application). To achieve the broad reaching effects taught by Rezai, it would not be an obvious design choice to stimulate an end organ as suggested in the Office Action. Further, comparison of (i) what might be an obvious design choice for treatment of classic sympathetic diseases and symptoms as discussed in Rezai with (ii) what might be obvious design choices with regard to treatment of diseases mediated by an immune response is not appropriate due to the differences between such disparate diseases.

At least for the reasons discussed above, claims 63-67 are not obvious in light of Rezai. Withdrawal of the rejection is respectfully requested.

2. Rezai in view of Tracey

Claims 18-42 and 66-70 have been rejected under 35 U.S.C §103(a) as allegedly being obvious over Rezai in view of Tracey (US 6,610,713). Applicant traverses the rejection to the extent it is maintained.

Applicant respectfully notes that it is unclear as to which claims are being rejected by the combination of Rezai and Tracey. The Office Action states that Tracey teaches that inflammatory mediators include TNF-α and cytokines. However, the subject matter of at least some of 18-42 and 66-70 do not appear to be directed to such subject matter, with claims 69 and 70 being cancelled at the time the Office Action was mailed. Regardless of the confusion, the following general comments are presented with regard to Rezai in view of Tracey.

Tracey fails to overcome the deficiencies of Rezai with regard to the independent claims, as discussed above. In fact, the combination of Rezai and Tracey would teach away from the independent claims. As stated above, Rezai does not recognize that stimulation of the sympathetic system (or a neuron thereof) can result in an anti-inflammatory effect. Tracey on the other hand teaches that stimulation of the parasympathetic system (or a neuron thereof) can result in an anti-inflammatory response. The sympathetic (fight or flight) and parasympathetic (rest and digest) nervous systems generally act in opposing fashion. Stimulation of the sympathetic system (or a neuron thereof) would be expected to produce a result that is vastly different fro stimulation of the

parasympathetic nervous system (or a neuron thereof). One of skill in the art would not look to stimulating a neuron of the sympathetic system to effectuate a physiological change similar to one shown to occur when stimulating the parasympathetic nervous system. Because of the antagonistic nature of these two systems, one would not have expected that stimulating a neuron of the sympathetic nervous system would result in inhibition of the release of a pro-inflammatory mediator or inhibition of an inflammatory cytokine cascade in a manner similar to the parasympathetic nervous system. In fact, one would have likely expected an *increased* inflammatory response if reviewing the disclosure or Rezai in light of Tracey. According the combined disclosures of Rezai and Tracey does not render obvious the independent claims or ay of the dependent claims to which the rejection was intended to apply.

Withdrawal of the rejection is respectfully requested.

3. King

Claims 1-4, 8-10, 15 and 54-67 have been rejected under 35 U.S.C §103(a) as allegedly being obvious over King (US 6,058,331). Applicant traverses the rejection to the extent it is maintained.

The Office Action states that King inherently teaches the methods of claims 1-4, 8-10, 15 and 54-67 because King teaches stimulation of the sympathetic neuron for treating ischemia and that ischemia is a disease or disorder mediated by the immune system. While Applicant does not ascribe to the logic presented in the Office Action, independent claim 1 has been amended to recite a list of disorders from which patients suffering from or at risk of may be identified. None of the recited diseases are ischemic diseases. Claim 54 has been amended to delete cerebral infarct, which the Office Action asserted was due to ischemia.

As stated above, the inventor of the present application recognized for the first time that stimulation of a sympathetic neuron may be used to attenuate an immune response or inhibit release of a pro-inflammatory mediator. It appears that nothing in the teachings of King would lead one to apply the teachings of King to subjects suffering from or at risk of the inflammatory disorders now recited in independent claims 1 and 54. Accordingly, claims 1 and 54, and their dependent claims 2, 3, 8-10, 15, and 55-67, are not obvious in light of King.

Withdrawal of the rejection is respectfully requested.

4. King in view of Tracey

Claims 18-42 and 66-70 have been rejected under 35 U.S.C §103(a) as allegedly being obvious over King in view of Tracey. Applicant traverses the rejection to the extent it is maintained.

Applicant respectfully notes that it is unclear as to which claims are being rejected by the combination of King and Tracey. The Office Action states that Tracey teaches that inflammatory mediators include TNF-α and cytokines. However, the subject matter of at least some of 18-42 and 66-70 do not appear to be directed to such subject matter, with claims 69 and 70 being cancelled at the time the Office Action was mailed. Regardless of the confusion, the following general comments are presented with regard to Rezai in view of Tracey.

One of skill in the art, upon reading King, would not be led to stimulate a sympathetic neuron to reduce inflammation in a subject suffering from or at risk of a disease or disorder recited in the independent claims of the present application. King does not appear to teach that stimulation of a neuron of the sympathetic system can result in inhibition of release of a pro-inflammatory mediator. While King does disclose that stimulation of a sympathetic ganglia (see, e.g., column 3, lines 45-48) may be useful for treating symptoms in patients with peripheral vascular disease to increase blood flow or decrease ischemic pain, King doe not appear to teach or recognize that such stimulation may reduce inflammation or an inflammatory response. One of skill in the art, upon reading King would not be lead to treat inflammatory aspects of a disease through sympathetic stimulation.

Tracey fails to overcome the deficiencies of King with regard to the independent claims, as discussed above. In fact, the combination of King and Tracey would teach away from the independent claims. As stated above, King does not recognize that stimulation of the sympathetic system (or a neuron thereof) can result in an anti-inflammatory effect. Tracey on the other hand teaches that stimulation of the parasympathetic system (or a neuron thereof) can result in an anti-inflammatory response. The sympathetic (fight or flight) and parasympathetic (rest and digest) nervous systems generally act in opposing fashion. Stimulation of the sympathetic system (or a neuron thereof) would be expected to produce a result that is vastly different fro stimulation of the parasympathetic nervous system (or a neuron thereof). One of skill in the art would not look to stimulating a neuron of the sympathetic system to effectuate a physiological change similar to one shown to occur when stimulating the parasympathetic nervous system. Because of the antagonistic

nature of these two systems, one would not have expected that stimulating a neuron of the sympathetic nervous system would result in inhibition of the release of a pro-inflammatory mediator or inhibition of an inflammatory cytokine cascade in a manner similar to the parasympathetic nervous system. In fact, one would have likely expected an *increased* inflammatory response if reviewing the disclosure or King in light of Tracey. According the combined disclosures of King and Tracey does not render obvious the independent claims or ay of the dependent claims to which the rejection was intended to apply.

Withdrawal of the rejection is respectfully requested.

5. Tracey in view of Sherwood

Claims 1-4, 18-42, 17, 54-62, 66-70 and 140-199 have been rejected under 35 U.S.C §103(a) as allegedly being obvious over Tracey in view of Sherwood, "Human Physiology: From Cells to Systems". Applicant traverses the rejection to the extent it is maintained.

The Office Action states that because Tracey teaches that stimulation of the parasympathetic system (or a neuron thereof) can attenuate an immune response or reduce the release of a proinflammatory mediator, it would have been obvious to stimulate the sympathetic system (or a neuron thereof) with parameters differing from Tracey to achieve an effect similar to that taught by Tracey because it is known from Sherwood that the balance between sympathetic tone and parasympathetic tone can be shifted either by increasing sympathetic activity or decreasing parasympathetic activity (or vice versa).

However, there are a few significant problems in the logic presented in the Office Action. First, the Office Action assumes that what holds for the global autonomic nervous system will apply with regard to local changes. That is, Tracey teaches stimulation of a particular parasympathetic nerve, the vagus nerve, can attenuate an inflammatory immune response. Based on the the teachings of Tracey and absent hindsight, it is unclear to Applicant (and Applicant asserts that it would be unclear to one of skill in the art) as to how to go about stimulating a sympathetic nerve to achieve a result similar to that achieved in Tracey via stimulation of the vagus nerve. What sympathetic nerve would one stimulate? What parameters should be used? Stimulating or inhibiting parameters?

Second, the parameters stated in the Examples Tracey for stimulating the vagus nerve (parasympatehteic) are very similar to those disclosed in the Example of the present application for

stimulation of the splenic nerve (sympathetic) with regard to frequency, which the Office Action points to as being important for accentuating or inhibiting the effects of a neuron. In Examples 2 (column 16, line 25) and 3 (column 18, line 24) of Tracey the vagus nerve was stimulated at a frequency of 1 Hz to inhibit inflammatory cytokine cascades. In the present application (paragraph 133 of the published application), the vagus nerve was stimulated at a frequency of 10Hz to achieve similar effects. Such results, even according to the logic of the Office Action, are unexpected in view of Tracey.

At least for the reasons stated above, claims 1-4, 18-42, 17, 54-62, 66-70 and 140-199 are not obvious over Tracey in view of Sherwood. Withdrawal of the rejection is respectfully requested.

6. Tracey in view of Sherwood in further view of Whitehurst

Claims 2-4 and 55-62 have been rejected under 35 U.S.C §103(a) as allegedly being obvious over Tracey in view of Sherwood in further view of Whitehurst et al. (US 6,735,475 - - herein Whitehurst). Applicant traverses the rejection to the extent it is maintained.

Whitehurst fails to overcome the deficiencies discussed above regarding Tracey and Sherwood. Whitehurst is cited in the Office Action for the proposition that it is well known to apply electrical signals via implantable pulse generators. This does nothing to overcome the deficiencies of Tracey and Sherwood with regard to the independent claims. Thus, dependent claims 2-4 and 55-62 are not rendered obvious by the combined teachings of Tracey, Sherwood and Whitehurst.

Withdrawal of the rejection is respectfully requested.

Double Patenting Rejection

Claims 1-4, 8-10, 15, 17-42, 54-67 and 130-199 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-69 of Application No. 10/820,937. Applicant traverses the rejection to the extent it is maintained.

A Notice of Abandonment was mailed on August 14, 2007 for Application No. 10/820,937. Thus, it appears that the present application and Application No. 10/820,937 are no longer copending. Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the foregoing, Applicants respectfully request reconsideration and allowance of the claims as all rejections have been overcome. Early notice of allowability is kindly requested.

Applicant believes that no fees are required for submission of this paper and associated documents. However, if any fees are required, the Commissioner is authorized to charge Deposit Account No. 50-3964 for fees in connection with this filing.

The Examiner is respectfully requested to contact the undersigned by telephone at 651.259.6704 or by E-mail at kcampbell@cnwiplaw.com with any questions or comments.

Respectfully submitted,

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